



Department of Pesticide Regulation



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May 23, 2007

TO: INTERESTED PARTIES

SUBJECT: *COMMENT PERIOD EXTENDED FOR REQUEST FOR COMMENTS ON ACTIVE INGREDIENTS PRIORITIZED FOR RISK ASSESSMENT INITIATION-*

In 2005, the Department of Pesticide Regulation (DPR) implemented a revised process for the selection of active ingredients (AIs) for risk assessment initiation. The goal of this process was to develop a ranked list of approximately 10 compounds from which DPR would select the AIs. As a result of that process, DPR adopted such a ranked list. This list and supporting information were presented to the Pesticide Registration and Evaluation Committee (PREC) and opened for public comment. That list is now being updated.

The Risk Assessment Prioritization Work Group (RAPWG) was formed to carry out this process and is made up of senior scientists from DPR's Medical Toxicology, Worker Health and Safety, and Environmental Monitoring Branches, as well as a senior scientist from both the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA). A number of factors are considered in the prioritization process. These factors include physical-chemical properties (vapor pressure, environmental persistence, water solubility, soil binding, bioconcentration potential, etc.), toxicological properties (no observed effect level- NOEL, severity of effect, number of effects, number of studies and species showing the effect, dose-response relationship, relevance of mechanism of action to humans, systemic vs. local effects, etc.), and exposure characteristics (types of exposures, amount of use, use patterns, number of crops and sites, locations of use, methods of application, types of formulations, illness surveillance data, availability of exposure data, etc.).

At the first RAPWG meeting held on October 18, 2006, the members of the RAPWG discussed the process that would be followed to create a ranked list of 10 AIs for risk assessment initiation by DPR. There was general agreement to select AIs that minimized duplication of the efforts of U.S. Environmental Protection Agency (U.S. EPA). The members of RAPWG would individually examine the chemicals remaining on the 2005 list and suggest any that should be removed (i.e. lowered in priority for risk assessment initiation) and suggest additional AIs for consideration. These suggestions were sent to the chair of the RAPWG.

No AIs were suggested for removal from the existing list. The AIs suggested in 2006 for initial consideration by the RAPWG were chlorthal dimethyl, diazinon, dicofol, formaldehyde, kresoxim-methyl, metofluthrin, propylene oxide, propyzamide, spirodiclofen, sulfur, sulfur dioxide, and tralkoxydim. The chair of the RAPWG prepared data packages on these AIs and sent them out on December 29, 2006, for consideration by the members of the RAPWG. Data packages were also included on the AIs that were considered but not selected by the RAPWG.



during the 2005 prioritization effort. These AIs were aldicarb, lambda cyhalothrin, oryzalin, oxydemeton methyl, oxyfluorfen, phorate, and phosmet. The packages included the Medical Toxicology Branch Summary of Toxicology Data for each active ingredient, toxicology fact sheets available from U.S. EPA, data on use, information on the status at U.S. EPA, data on physical-chemical properties, data on illness incidences and exposure characteristics, relevant information available from the Agency for Toxic Substances Disease registry (ATSDR), and fact sheets from the Extension Toxicology Network (EXTOXNET) or the National Pesticide Information Center (NPIC).

A meeting of the RAPWG was held on January 24, 2007. At this meeting, the first discussion topic related to the AIs still on the prioritization list from the last (2005) RAPWG effort. These AIs are acrolein, boric acid, linuron, and propanil. After some discussion there was a consensus that all four should remain on the list. There was some discussion as to whether to remove boric acid, based on U.S. EPA's recent assessment. It was decided that potential residential exposures to boric acid were still of concern; however, there was agreement that when the risk assessment is conducted by DPR, duplication of effort should be avoided and maximum use should be made of existing evaluations and risk assessments, notably those conducted by U.S.EPA. In fact, there was general agreement that this should be true for all risk assessments conducted by DPR. It was noted that acrolein would be assigned for risk assessment initiation in the near future. Therefore, seven additional AIs were needed to bring the total up to ten (the desired number).

The RAPWG next discussed each of the AIs that were considered, but not selected, by the RAPWG during the last prioritization effort. Following the discussion of candidates from 2005, the RAPWG discussed each of the new candidates. There was extensive discussion of sulfur, for which the primary concerns were skin and eye irritation, rather than the more traditional systemic toxicity (which is very low). It was decided that a traditional risk assessment would not be very productive and that there were other avenues to address use practices. There was extensive discussion regarding the new AI, metofluthrin (a pyrethroid that will be used as a mosquito repellent). While there was concern regarding neurotoxicity (tremors) and the inhalation route of exposure, it was noted that specific products had not yet been registered. As a result, this AI will be considered at the next prioritization effort, at which time there are expected to be registered products.

Following discussion of the various AIs, there was a general consensus that dicofol, propyzamide, spiroticlofen, sulfur dioxide, diazinon, and lambda-cyhalothrin should be included. After some discussion, the group could not choose between phosmet and chlorthal-dimethyl, so it was suggested that both be included and the one that got the lowest priority be dropped. Following the meeting, it was noted that U.S. EPA released a final decision on phosmet (notice dated January 18, 2007) that includes numerous risk mitigation measures including phase-outs. As a result, phosmet was removed from the ranking procedure.

As was the case with the 2005 RAPWG process, the next step was for each of the members of the RAPWG to rank the AIs, with 1 going to the highest priority AI. The individual rankings were combined (averaged for each AI), resulting in an overall ranking. The overall ranking is as follows (same number indicates tie ranking):

1. Dicofol
2. Diazinon
3. Propanil
4. Propyzamide (pronamide)
5. Linuron
6. Spirodiclofen
7. Lambda cyhalothrin
8. Chlorthal-dimethyl
9. Boric acid
10. Sulfur dioxide

A one to two page draft document was prepared for each of the ten chemicals. Each document provides a brief summary of the toxicology data, physical/chemical and environmental characteristics, use information, exposure information, and the RAPWG's rationale for prioritizing the chemical for risk assessment initiation. These documents are only intended to provide some insight into the selection of the chemicals, as opposed to being any sort of complete or comprehensive description of the chemicals. A much more comprehensive description will be part of the risk assessment. It should also be noted that some of the toxicological conclusions and values (no observed effect level, NOEL; lowest observed effect level, LOEL) might change with the more in-depth evaluation that will take place in the risk assessment. These summaries were sent to the members of the RAPWG for their review and comment. Their comments were incorporated and the summaries are attached to this document.

On March 16, 2007, this information was presented to the PREC. This information is now being released for public comment. Comments are sought primarily on the choice of the active ingredients and their ranking. However, comments are also welcomed on the short summaries prepared for each AI. Following the close of the comment period, the RAPWG will meet to discuss the comments and whether changes should be made to the list of chemicals, the rankings, or to the summaries. When the RAPWG has finalized its recommendations, this information will be presented to DPR management. Following management acceptance of or modification to the list, a public notice will be released that includes the final group of chemicals, their rankings, the summaries, and responses to comments.

DPR is seeking comments on the choice of the ten active ingredients and their ranking. If you think an active ingredient should not have been included, please include the basis for your conclusions. It will also assist the process if you indicate the active ingredient that should replace

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it. Likewise, if you think a different active ingredient should have been included on the list, please indicate the basis for your conclusion and indicate the active ingredient that it should replace. The comment period will be open until June 15, 2007. Please send your comments to Dr. Jay Schreider by electronic mail jschreider@cdpr.ca.gov or to the address indicated below:

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Information Summaries on Active Ingredients Selected by Risk Assessment Prioritization Work Group

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Boric Acid

Background, Chemistry and Use

CAS # 10043-35-3

H_3BO_3

For the purposes of toxicity and risk evaluation, boric acid is grouped with its sodium salts. These salts include sodium tetraborate ($\text{Na}_2\text{B}_4\text{O}_7$, borax) and its hydrates, sodium metaborate (NaBO_2) and its hydrates, and disodium octaborate ($\text{Na}_2\text{B}_8\text{O}_{13}$) and its hydrates.

Boric acid and its salts are registered for use as insecticides, algacides, fungicides, herbicides, and wood treatments. It is used on a variety of agricultural and nonagricultural (including indoor residential) sites. As an insecticide, it functions as a stomach poison as well as an abrasive on insect exoskeletons. As an herbicide, it functions as a desiccant. Depending on the specific active ingredient and intended use, formulated products may be solids, crystalline rods, powders, dusts, gels, liquids, pastes, baits, and granules. Over 1.4 million pounds of boric acid and its salts were reported sold in California in 2002.

In addition to medicinal uses (primarily as a disinfectant), the nonpesticidal uses of boric acid and its salts are extensive and include use in a variety of industrial processes as well as fire control. In addition, boric acid and its salts are ubiquitous in the environment, due to the ubiquitous nature of boron in the environment. Boron occurs naturally in water, fruits, and vegetables. Boric acid and its salts are solids. Boric acid has a low volatility, is stable in the environment, and highly soluble in water. The U.S. EPA completed a risk assessment (Reregistration Eligibility Document, RED) on boric acid in 1993 and released a Tolerance Reassessment Eligibility Document (TRED) in 2006.

Toxicity

Boric acid has a relatively low acute toxicity by the oral route, with a lethal dose to 50 percent of the animals in the test groups (LD_{50} s) well over 1000 mg/kg in laboratory animals. However, lethality has occurred in infants after oral ingestion of amounts in the range of 3-6 grams. The dermal toxicity of boric acid is low for intact skin, due to the low dermal absorption. However,

absorption in damaged skin occurs much more readily. Earlier uses of boric acid in baby powder resulted in fatalities. The ocular toxicity of boric acid and most of its salts is low; however, sodium tetraborate is highly toxic to the eye.

In laboratory animals, boric acid has been shown to cause reproductive and developmental toxicity. In oral chronic and subchronic toxicity studies in dogs, boric acid caused testicular atrophy and adverse effects on sperm. In rat oral chronic toxicity studies, boric acid and its salts again caused testicular atrophy with NOELs in the range of 350 ppm (in food) in terms of elemental boron. A mouse oncogenicity study indicated a no observed adverse effects levels (NOAEL) of 2500 ppm boric acid for testicular atrophy. There were no indications of oncogenic effects and U.S. EPA has classified boric acid as a Group E, evidence of noncarcinogenicity. In a multi-generation rat reproduction study, testicular atrophy, lack of viable sperm, and impaired reproduction were noted. The NOAEL was judged to be 150 mg/kg by USEPA in their RED. In a mouse reproduction study, a variety of adverse testicular and reproductive effects were seen with a NOEL of 1000 ppm boric acid. In a rat developmental toxicity study, boric acid caused developmental effects (increased incidence of wavy ribs, shortened rib, and reduced fetal weight) at a NOAEL of 750 ppm boric acid in the diet. A rabbit developmental toxicity study indicated a NOEL of 62.5 mg/kg for a variety of malformations. Likewise, a mouse developmental toxicity study indicated malformations. Genotoxicity studies were generally negative.

Human epidemiology studies of occupationally exposed individuals did not indicate adverse impacts on fertility; however, the studies did have limitations.

Basis for Selection

Boric acid was originally assigned a moderate priority in the “Prioritization and Status of Active Ingredients for Risk Characterization,” due to the relatively high levels at which adverse effects occurred. However, while the developmental and reproductive effects occurred at relatively high dose levels, the effects were repeatable in a variety of animal species and the same species in different studies. There is use in a variety of settings, including indoor residential use. In addition, boric acid has often been put forward as a “safe” alternative to other pesticides in these same settings, which could lead to less careful use practices, resulting in potentially high exposures. With this in mind, it was judged to be prudent to evaluate the associated risks from these various uses; therefore, boric acid was prioritized for risk assessment initiation. In order to avoid duplication of effort, maximum use will be made of existing U.S. EPA evaluations and risk assessments.

Linuron

Background, Chemistry and Use

CAS # 330-55-2

3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea

U.S. EPA completed a Reregistration Eligibility Document in 1995 and a Tolerance Reassessment in 2002.

Linuron is an herbicide in the substituted urea class. It is intended to control germinating and newly emerged grasses and broad-leaved weeds. It is registered for agricultural uses with no residential/consumer uses. Of the approximately 71,000 pounds reported as used in California in 2005, approximately 58,000 pounds were used on carrots, 7,000 on asparagus, and 5,000 on celery.

The pure compound is an odorless white solid with a low vapor pressure. Linuron is moderately persistent in soils with half-lives reported from 30 to 150 days, depending on the soils and conditions. It is generally immobile in soil but mobility can increase under certain circumstances. It is slightly to moderately soluble in water and is moderately persistent. Because of its slight to moderate solubility, persistence, and mobility under some circumstances, it has the potential to impact groundwater.

Toxicity

Linuron does not have a high acute toxicity. Oral LD₅₀s are reported in the range of 1200 to 2250 mg/kg in rats and rabbits. The dermal LD₅₀ in rabbits is reported to be greater than 5000 mg/kg. It is a skin sensitizer. The acute toxicity is also low by the inhalation route.

Dietary exposure of rats in a developmental toxicity study indicated a NOEL of 125 ppm (equivalent to approximately 6.25 mg/kg) for maternal effects (decreased weight gain) and developmental effects (slight increases in skeletal abnormalities). A gavage study in rabbits indicated a NOEL of 25 mg/kg for maternal toxicity (decreased weight gain, liver hypertrophy, increased abortions) and limited evidence of skeletal irregularities in the fetuses. While the evidence of developmental effects was limited, the maternal effects indicated increased toxicity with repeated doses, as compared to the acute toxicity. In a multigeneration rat reproduction study, non-reproductive effects (decreased body weight gain and food consumption) were seen with a NOEL of 12.5 ppm (equivalent to approximately 0.63 mg/kg). Various abnormalities of the testes were observed with a NOEL of 100 ppm (equivalent to approximately 5 mg/kg). In addition, increased estradiol and luteinizing hormone levels were seen at the high dose of

625 ppm (31 mg/kg) suggesting endocrine activity. Ocular lesions were seen at the high dose. Pup viability was reduced at 100 ppm. A follow up study supported the endocrine disrupting activity. Another multigeneration rat reproduction study indicated a NOEL of 25 ppm for decreased parental weight gain and a NOEL of 125 ppm for smaller litters and decreased survival of pups. An ancillary study to this latter study maintained some of the animals on treatment for two years and indicated testicular interstitial cell adenomas and hyperplasia at 125 and 625 ppm.

A dog chronic feeding study indicated a NOEL of 25 ppm (equivalent to approximately 0.63 mg/kg) for blood effects (blood cell turnover and destruction). A chronic rat feeding study indicated testicular interstitial cell adenomas and indications of blood cell turnover and destruction, with a NOEL of 50 ppm (2.5 mg/kg). An ancillary study, related to the prior study also indicated testicular interstitial cell tumors. A mouse oncogenicity study indicated hepatic toxicity in both sexes as well as hepatocellular adenomas in females at 1500 ppm (225 mg/kg). Various studies did not indicate genotoxicity.

Basis for Selection

Linuron was prioritized for risk assessment due to its relatively low NOELs for toxicity from repeated exposures, reproductive toxicity demonstrated in several studies, testicular adenomas seen in a repeated rat chronic toxicity study, and endocrine disrupting activity.

Propanil

Background, Chemistry and Use

CAS # 709-98-8

3',4'-dichloropropionanilide

C₉H₉Cl₂NO

Propanil is a broad spectrum, post-emergent herbicide. In California, it is used almost exclusively on rice. It is applied both aerially and by ground boom. It is a California restricted material because it has a history of drift, resulting in damage to crops in fields adjacent to the rice fields. Use has expanded significantly since 1997, due, in part, to changes in use regulations. In 2005, approximately 1,400,000 pounds were reported as used in California. Of this total, all but about 30 pounds were reported used on rice. U.S. EPA published a risk assessment for Propanil in 2002; however, this assessment did not address the risk to bystanders (people living near rice fields) from the offsite movement of Propanil.

Propanil technical is a brown crystalline solid with a low vapor pressure (9×10^{-7} mm Hg). It is rapidly broken down in the soil and water due to microbial activity. It has a field half-life of 1 to 3 days. It is soluble in water and only weakly adsorbs to soil particles, indicating soil mobility. Propanil has been found in surface water in California.

Toxicity

Propanil has relatively low acute toxicity. Reported oral LD₅₀s are approximately 1000 mg/kg or higher for rats and dogs. It can cause eye and skin irritation. A reported 4-hour LC₅₀ in rats is 1.12 mg/L. In a rat developmental toxicity study, the maternal NOEL was 100 mg/kg, the highest dose tested. In a rabbit developmental toxicity study, the maternal NOEL was 20 mg/kg for increased mortality and decreased body weight at 100 mg/kg. The body weight changes were measured after 6 days of exposure; however, there is no way to tell if the effects occurred due to a single or multiple (6) exposures. Similar body weight changes were seen in rat pilot studies after similar timeframes, but with the same caveat regarding a single exposure. There are a number of studies in the open literature reporting the immunotoxicity of propanil after a single dose of propanil in rats and mice.

A 90-day oral study in rats indicated a NOEL of approximately 33 mg/kg for increased relative spleen weights and decreased hemoglobin levels. A 90-day oral study in mice indicated a NOEL of approximately 7 mg/kg for liver toxicity. A multigeneration oral rat reproduction study indicated a parental NOEL of 150 ppm (in food, equivalent to approximately 7.5 mg/kg) for

decreased body weight, increased spleen weights, increased brain weights, increased testes weights, increased adrenal weights, increased ovary weights, and increased pigmented spleen macrophages at 600 ppm. The reproductive NOEL was 150 ppm for decreased sperm counts. The pup NOEL was 150 ppm for increased liver and testes weights, decreased pup weights, and delayed vaginal perforation and balanopreputial separation. These latter effects, along with the testes and sperm effects, suggest the possibility of neuroendocrine disruption.

A chronic dog feeding study had a LOEL of 200 ppm (approximately equivalent to 5 mg/kg) for several hematological parameters (including methemoglobinemia and red blood cell hemolysis), decreased body weight gain, and increased hemosiderin pigment in the kidneys. A chronic oral rat study had a NOEL of 200 ppm (10 mg/kg) for non-oncogenic effects including decreased body weight, decreased food consumption, methemoglobinemia, increased spleen weights, congested spleen, various signs of liver toxicity, testicular hyperplasia, absent spermatozoa, prostate atrophy, and hemosiderin pigment in spleen and kidneys. There was also an increased incidence of testicular interstitial cell tumors in males and hepatocellular adenomas in females. An oral mouse oncogenicity study had a NOEL of 500 ppm (approximately equivalent to 75 mg/kg) for methemoglobinemia and increased spleen weights. There was also an increased incidence of malignant lymphoma. Genotoxicity studies were negative.

Basis for Selection

Propanil was prioritized for risk assessment initiation due to its relatively high use, its demonstrated potential for offsite movement, the potential for bystander exposure, including people living near rice fields, and its demonstrated long-term toxicity. This toxicity included methemoglobinemia and other blood effects, cancer, endocrine effects, and possible immunotoxicity.

Chlorthal dimethyl (DCPA, dacthal)

Background, Chemistry and Use

CAS # 1861-21-1

Dimethyl tetrachloroterephthalate

$C_{10}H_6Cl_4O_4$

DCPA is a pre-emergent herbicide for the control of grasses and broadleaf weeds and is used in California primarily on row crops. In 2005, a total of approximately 226,000 pounds were reported used in California. Of this, approximately 106,000 were used on broccoli, 64,000 pounds on onions, 14,000 pounds on cauliflower, 6,000 on rappini, 4,000 on turf and sod, with the remainder on a variety of other crops. There are both commercial and residential uses. A Reregistration Eligibility Document was completed by U.S. EPA in 1998.

Pure DCPA is a white or colorless crystal that melts at 155° C. While DCPA itself is not very persistent or mobile in the environment, its two environmental breakdown products, tetrachloroterephthalic acid (TPA), the primary breakdown product) and monomethyl tetrachloroterephthalic acid (MTP), are environmentally mobile and persistent, with the potential to leach to groundwater. TPA has been found in groundwater in many areas of the State. DCPA can volatilize from soil and has been a source of DCPA residues on crops to which it has not been applied. Hexachlorobenzene (HCB), classified by U.S. EPA as a probable human carcinogen, is a manufacturing impurity in DCPA; however, more recent manufacturing methods have reduced HCB concentrations.

Toxicity

DCPA has low acute toxicity. The oral LD₅₀ in the rat is over 5,000 mg/kg; the acute dermal LD₅₀ is over 2,000 mg/kg; and DCPA is not an apparent skin sensitizer. Dietary exposure of rats in a developmental toxicity study indicated a maternal NOEL of 1,000 mg/kg for decreased weight gain, with no developmental toxicity at the highest dose tested (2,000 mg/kg). In the rabbit developmental toxicity study, the NOEL for maternal toxicity was 250 mg/kg with severe maternal toxicity (including death) at 500 mg/kg. There were no signs of developmental toxicity other than increased resorptions in the does that died. A developmental toxicity study on TPA in rats indicated mild maternal toxicity at 1,250 mg /kg and higher and no developmental effects. A two-generation rat reproduction study had a pup NOEL of 1,000 ppm for decreased body weight. A 90-day rat study had a NOEL of 50 mg/kg for histological effects in the kidneys, lung, and liver. A 90-day rat study using TPA had a NOEL at least 500 mg/kg.

A 2-year rat chronic/oncogenicity study had a NOEL of 1 mg/kg for liver hyperplasia effects and thyroid effects, a NOEL of 500 mg/kg for lung lesions and retinal effects, and hepatocellular tumors at 500 mg/kg. A follow up rat chronic study looking in more detail at possible ophthalmological effects and using doses up to 1,000 mg/kg did not show any retinal effects. A 2-year mouse chronic/oncogenicity study had a NOEL of 1,000 ppm (510 mg/kg in females) for liver effects and hepatocellular tumors at the high dose of 7,500 ppm (1,141 mg/kg in females). Genotoxicity studies were essentially negative. U.S. EPA classified DCPA as a possible human carcinogen and generated a cancer potency factor (Q_1^* of 1.49×10^{-3}) based on the rat liver tumors.

Basis for Selection

DCPA was prioritized for risk assessment initiation due to its moderate use on food crops, its potential to contaminate groundwater, its volatilization properties, and its potential carcinogenic effects.

Diazinon

Background, Chemistry and Use

CAS # 333-41-5

O, O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate

C₁₂H₂₁N₂O₃PS

Diazinon is an organophosphate insecticide, and the technical form of the AI is an amber to brown liquid with a boiling point of 83-84°C. It is not very soluble in water but is very soluble in a variety of organic solvents. It has a low potential for movement to groundwater.

Diazinon has registered uses on a wide variety of crops, including row crops, tree fruits, and nuts. In 2005, a total of 397,000 pounds were reported as used in California. Of this total, approximately 155,000 pounds were used on lettuce, 34,000 pounds on almonds, 27,000 pounds on broccoli, 22,000 pounds on spinach, and 19,000 pounds each on peaches and prunes.

Before 2002, diazinon had widespread residential uses. Due to an agreement between U.S. EPA and the registrants, indoor product registrations were cancelled in 2002 and outdoor residential product registrations were cancelled in 2004. U.S. EPA released an Interim Reregistration Eligibility Document (IRED) in 2002 and a revised IRED in 2004. U.S. EPA evaluation of diazinon as part of the cumulative risk assessment organophosphate insecticides was finalized in 2006.

Toxicity

Diazinon is neurotoxic and exerts its primary toxic effects through the inhibition of the enzyme, acetylcholinesterase. Acute toxicity studies indicated an oral LD₅₀ of 1250 mg/kg, a dermal LD₅₀ of >2020 mg/kg, and an inhalation LC₅₀ of > 2.33 mg/L/ 4 hours. An acute oral neurotoxicity study in rats indicated a NOEL of < 2.5 mg/kg. A 90-day neurotoxicity feeding study in rats indicated a NOEL of 0.3 ppm (approximately 0.01 mg/kg) for inhibition of brain cholinesterase. A 21-day whole body rat inhalation study had a LOEL of 0.1 ug/L (6 hours/day) for RBC and serum cholinesterase inhibition. Developmental toxicity studies in the rat and rabbit did not demonstrate adverse developmental effects. A two-generation rat reproduction study indicated a NOEL of < 10 ppm for decreased pup survival and body weights. A rat chronic toxicity study had a NOEL of 0.1 ppm for serum cholinesterase and 1.5 ppm for red blood cell and brain cholinesterase, with no clinical signs of neurotoxicity. A dog chronic toxicity study had a NOEL of 0.1 ppm (approximately 0.004 mg/kg) for serum cholinesterase and 0.5 ppm (approximately

0.02 mg/kg) for decreased body weight. Mouse and rat oncogenicity studies did not demonstrate any possible carcinogenic effects.

DPR recently completed the monitoring phase of a year-long project in the Central Valley town of Parlier. In that project, DPR monitored the ambient air for a number of pesticides. During the twelve-month monitoring period, diazinon was found in 32% of the ambient air samples.

Basis for Selection

Diazinon was prioritized for risk assessment initiation due to its widespread use, toxicity profile, low NOELs, and demonstrated potential for exposure through the ambient air. While U.S. EPA has completed several evaluations involving diazinon, ambient air exposure has not been evaluated, at least not with data as extensive as that derived from the Parlier study. In its risk assessment, DPR will maximize the use of existing evaluations in order to avoid duplication of effort and to complete its assessment in a timely manner.

Dicofol

Background, Chemistry and Use

CAS # 115-32-2

1,1-bis(chlorophenyl)-2,2,2-trichloroethanol

C₁₄H₉Cl₅O

Dicofol is an organochlorine insecticide/miticide that is structurally similar to Dichloro-Diphenyl-Trichloroethane (DDT). Older technical grades contained higher concentrations of DDT as a manufacturing contaminant; however, newer technical grades have significantly reduced the amount of DDT and related contaminants. Dicofol is used on a variety of crops in California, but primarily on cotton. In 2005, approximately 194,000 pounds were reported used in California, with 131,000 pounds reported as used on cotton, 21,000 pounds on oranges and other citrus crops, 10,000 pounds on beans, and 9,000 on walnuts.

U.S. EPA released a Reregistration Eligibility Document (RED) on dicofol in 1998. Technical dicofol is a reddish-brown viscous liquid with a low vapor pressure. It is insoluble in water but is soluble in organic solvents. Dicofol is moderately persistent in the environment, depending on the acidity of the soil, being more persistent in acidic soil. It is not mobile in soil.

Toxicity

Dicofol is not highly acutely toxic, with an inhalation LC₅₀ in rats of 4.2 mg/L and an oral LD₅₀ in rats of 587 mg/kg. Dicofol interferes with nerve transmission in mammals and overexposure can cause neurotoxic effects. A 90-day subchronic rat feeding study had a NOEL of 1.0 ppm (approximately 0.07 mg/kg) for liver and thyroid hypertrophy. A 90-day mouse feeding study had a NOEL of 10 ppm (1.6 mg/kg) for liver hypertrophy. A subchronic dog study had a NOEL of 10 ppm (0.29 mg/kg) for liver necrosis, myocardial necrosis, sperm effects, and testes effects. A rat developmental toxicity study did not indicate developmental effects, while a rabbit developmental toxicity study indicated increased abortions at 40 mg/kg with a NOEL of 4 mg/kg.

A two-year chronic rat study had a NOEL of 4.5 ppm (approximately 0.25 mg/kg) for various histopathological signs of liver toxicity. A chronic dog study had a NOEL of 30 ppm (0.84 mg/kg) for liver hypertrophy and a NOEL of 5 ppm (0.12 mg/kg) based on inhibition of ACTH stimulated cortisol release. A mouse oncogenicity study indicated increased incidences of liver adenomas at both dose levels of 471 and 942 ppm in males and 122 and 243 ppm in females. U.S. EPA classified dicofol as a possible human carcinogen due to its tumorigenic effects in

mice. A two-generation reproduction study in rats had a NOEL of 25 ppm for decreased pup survival and 5 ppm for liver hypertrophy in the parents, vacuolization of ovarian stromal cells in females. Genotoxicity studies submitted to DPR were negative.

Basis for Selection

Dicofol was prioritized for risk assessment due to its environmental persistence, structural similarity to DDT, liver toxicity at relatively low does levels in several species, reproductive effects, and tumorigenic effects.

Lambda Cyhalothrin

Background, Chemistry and Use

CAS # 91465-08-6

(RS)-alpha-cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoropropenyl)-2,2,-dimethylcyclopropanecarboxylate

$C_{23}H_{19}ClF_3NO_3$

Lambda cyhalothrin is a pyrethroid insecticide/miticide and is made up of two of the four isomers of the pyrethroid cyhalothrin. Lambda cyhalothrin is used on a variety of crops with a total of approximately 37,000 pounds reported used in California in 2005. Of this total, approximately 14,000 pounds were reported as used in structural pest control, 7,000 pounds on alfalfa, and 5,000 pounds on lettuce. In addition, lambda cyhalothrin is found in a number of residential use formulations. Technical lambda cyhalothrin is a solid at room temperature, has a low vapor pressure and low water solubility, but is soluble in a number of organic solvents. It binds tightly to soil and is moderately persistent in the environment.

Toxicity

Lambda-cyhalothrin was prioritized for risk assessment initiation based on its relatively low NOELs for neurotoxicity in several animal species and studies, its carcinogenic potential (albeit equivocal), and its use in a variety of structural and residential settings.

Propyzamide (pronamide)

Background, Chemistry and Use

CAS # 23950-58-5

3,5-dichloro-N- (1,1-dimethylpropynyl) benzamide

$C_{12}H_{11}NOCl_2$

Propyzamide (also known as pronamide) is an herbicide. Of the approximately 116,000 pounds reported used in California in 2005, about 108,000 pounds were reported as used on lettuce. It is a white solid at room temperature and has a low vapor pressure. It is relatively insoluble in water, but is soluble in several organic solvents. It is reported to be relatively persistent and binds to soil. U.S. EPA completed a Reregistration Eligibility Document on pronamide in 1992 and a Tolerance Reassessment Eligibility Document in 2002.

Toxicity

Pronamide has low acute toxicity, with an oral LD_{50} in rats of $>5,000$ mg/kg, a dermal LD_{50} of $>2,000$ mg/kg, and a 4 hour inhalation LC_{50} of >2.5 mg/L. A 4-week oral rat study indicated histopathological signs of liver toxicity at 500 ppm (about 40 mg/kg). A 90-day oral rat study had a NOEL for similar effects at 200 ppm (about 12 mg/kg). A rabbit developmental toxicity study had a maternal NOEL of 5 mg/kg for hepatocellular toxicity and clinical signs of toxicity and a NOEL of 20 mg/kg for abortions. A rat multigeneration study had a parental NOEL of 200 ppm (about 16 mg/kg) for decreased body weight as well as histopathological signs of toxicity in the liver, thyroid, adrenal, and pituitary glands.

A chronic dog study had a NOEL of 300 ppm (about 12 mg/kg) for decreased body weight, changes to clinical chemistry, increased thyroid weights, and histological changes to the liver, thyroid, ovaries, and kidney. A chronic oral rat study had a NOEL of 200 ppm (about 8.5 mg/kg) for increased liver weight and histological changes to the liver, thyroid, ovaries, and testes. The study also showed thyroid follicular cell adenomas at 1,000 ppm (about 43 mg/kg). Another chronic rat study had a NOEL of 200 ppm for decreased body weight and benign interstitial cell tumors in the testes and adenomas in the ovaries. Several supplementary rat studies indicated that pronamide interrupted the pituitary-testes endocrine axis. A chronic mouse study had a systemic NOEL of 5 mg/kg for gross findings in the liver and kidneys as well as decreased body weight gain. There was an increased incidence of hepatocellular adenomas and carcinomas at the high dose of 250 mg/kg. Two other chronic mouse studies also showed liver neoplasia. The genotoxicity studies were negative. U.S. EPA classified pronamide as a B2, "probable human

carcinogen,” and pronamide is also listed under Proposition 65 as “known to the state to cause cancer.”

Basis for Selection

Pronamide was prioritized for risk assessment initiation based on its liver and thyroid toxicity in several species, its endocrine disruption potential, and its consistent carcinogenic potential (demonstrated in two species and several studies).

Spirodiclofen

Background, Chemistry and Use

CAS # 148477-71-8

3-(2,4-dichlorophenyl)-2-oxo-1—oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate

C₂₁H₂₄Cl₂O₄

Spirodiclofen is one of a new class of insecticides called tetrone acid insecticides and is primarily intended for use as an acaricide (miticide). Since it is a new insecticide, there is a limited history of use; however, it is intended for use on a variety of crops. It is a solid at room temperature, has a low vapor pressure, and is soluble in a variety of organic solvents. It has a high soil adsorption and is expected to be moderately persistent in soil. It was conditionally registered by U.S. EPA in 2005.

Spirodiclofen exerts its effects by inhibiting lipid biosynthesis, which in turn interferes with steroid biosynthesis. In insects, this affect inhibits insects' ability to develop and to reproduce. This mode of action is also responsible for its toxicological effects in animal studies.

Toxicity

Spirodiclofen has low acute toxicity, with oral and dermal LD₅₀s > 2,000 mg/kg and an inhalation LC₅₀ > 5 mg/L. It does cause dermal sensitization. A subchronic oral rat study had a NOEL of 100 ppm (about 8.1 mg/kg) for histopathological effects in the adrenal glands. A Subchronic oral mouse study had a NOEL of 100 ppm (about (15 mg/kg) for histopathological effects in the testes and adrenal glands. A subchronic oral dog study had a NOEL of 200 ppm (about 8 mg/kg) for decreased body weight gain, increased liver and adrenal gland weights, and histopathological findings in the adrenal glands, testes, thymus, and prostate. Standard rat and rabbit developmental toxicity studies did not indicate developmental toxicity. U.S. EPA concluded that a rat developmental neurotoxicity study had a LOEL (no NOEL) of 70 ppm (about 6.5 mg/kg) for a decrease in memory in a water maze test. DPR did not reach this same conclusion and did not identify this effect in its review of the same study.

A two-generation reproduction study in rats had a parental NOEL of 70 ppm (about 5 mg/kg) for decreased body weight, decreased liver weight, decreased cholesterol, and histopathological effects on the adrenal glands. The reproductive NOEL was 350 ppm (about 26 mg/kg) for delayed sexual maturation, effects on sperm, testicular atrophy, histopathological effects in the uterus, and decreased body weight in the pups. A chronic oral dog study had a NOEL of 50 ppm (about 1.4 mg/kg) for increased adrenal weights, increased testes weights, and histopathological

effects in the adrenal glands and testes. A chronic oral rat study had a NOEL of 350 ppm (about 15 mg/kg) for decreased body weight, decreased cholesterol, and histopathological effects in the testes and uterus. In addition, the study showed an increased incidence of testicular adenomas and uterine adenomas and carcinomas. A chronic mouse study had a NOEL of 25 ppm (about 4 mg/kg) for increased liver and adrenal weights, discolored testes and adrenal glands, and histopathological effects in the testes, adrenal glands. This study also showed an increased incidence of hepatocellular adenomas and carcinomas. Genotoxicity studies were negative. U.S. EPA has classified Spirodiclofen as a probable human carcinogen.

Basis for Selection

Spirodiclofen was prioritized for risk assessment initiation due to its potential use as a miticide on a variety of crops, its endocrine disruption, and its reproductive, and carcinogenic effects in several studies and species.

Sulfur Dioxide

Background, Chemistry and Use

CAS # 7446-09-5

SO₂

Sulfur dioxide is a colorless gas with a pungent odor. It is soluble in water and organic solvents. Sulfur dioxide has pesticidal use as a fumigant. In 2005, approximately 170,000 pounds were reported as used in California and almost all of this use was on grapes or in winemaking. Sulfur dioxide's pesticidal uses include postharvest for golden raisins (to prevent browning), for table grapes in storage, and in some winemaking processes. It is also used to fumigate wood barrels prior to use for holding wine.

Sulfur dioxide is also a combustion byproduct and is a major contributor to air pollution. There are also natural sources of atmospheric sulfur dioxide. It is a criteria air pollutant and has been reviewed as an air pollutant by a number of state and federal agencies (U.S. EPA; Agency for Toxic Substances Disease Registry, ARB; OEHHA, etc.). Because of its status as a major air pollutant, there is a large body of toxicological data on sulfur dioxide. Much of this data is based on human studies, either epidemiological or, in some cases, controlled human exposures. There is also a toxicological database from studies on laboratory animals.

Toxicity

Acute exposures to high levels of sulfur dioxide (e.g. 100 ppm) are life threatening. Sulfur dioxide is a respiratory irritant and short-term exposures to lower concentrations can affect breathing and may aggravate existing respiratory and cardiovascular problems. Asthmatics are especially susceptible to the irritant effects and respiratory difficulty resulting from sulfur dioxide exposure. Longer-term exposure to sulfur dioxide can adversely affect lung function, structure, and resistance to infection.

Basis for Selection

Sulfur dioxide was prioritized for risk assessment initiation because of its potential for inhalation exposure and for causing adverse respiratory effects in people. From the use numbers, it can be seen that the pesticidal uses of sulfur dioxide are insignificant contributors to the overall sulfur dioxide ambient air pollution. Risk assessment of sulfur dioxide by DPR would only address its pesticidal use and the risk directly attributable to this use.